BS

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,309	06/06/2001	Masayoshi Mishina	55573	8081

21874 7590 11/01/2004

EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,309	MISHINA ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) *8,10-13,15-18 and 20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,10-13,15-18 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/04 and 09/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments received 09/28/2004 have been entered. Claims 9,14 and 19 have been cancelled. Claims 8,10,13,18, and 22 have been amended. Claims 8,10-13,15-18 and 20-22 are pending and are under current consideration.

Claim Objections

Claims 8,13 and 18 are objected to because of the following informalities:

The language of claims 8 and 13 is grammatically improper and should be clarified. Method step (d) reads "growing the fertilized eggs to embryos of mutant having a gene having small deletion of a plurality base pairs around the crosslinked site in a genome." The terminology "embryo of mutant" is unclear language. Articles and prepositions are missing from the phrase.

The language of claim 18 is grammatically unclear. Step (d) recites the phrase "growing the fertilized eggs to a mutant having a mutated gene". The phrase fails to set forth what "a mutant" is referring to. The claim is interpreted as referring to "a mutant vertebrate animal". Step (e) recites the phrase "wild type of the vertebrate animal", which is grammatically unclear.

Appropriate correction is required.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8,10-13, 15-18 and 20-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant's arguments have been fully considered and are found partially persuasive.

Applicant's amendments to the claims are sufficient to overcome the rejection of claims 8,13 and 18 on the grounds that the claims appear to be directed to fertilization of sperm (page 3, paragraph 3 of the previous office action), and of claim 18 on the grounds that there is insufficient antecedent basis for the limitations "the mutated gene", the treated germ cell", the said differences of phenotype", and for omitting the step of creating a mutant animal (see previous office action at page 4, paragraphs 1-4).

The rejection of claims 8 (and dependent claims 10-12) and 13 (and dependent claims 15-17) as being incomplete is withdrawn in light of Applicant's amendments to the claims. The claims now contain a step of growing fertilized eggs to an embryo comprising a mutant gene.

The previous rejection of claims 18 and 20-22 as being indefinite because the comparison step requires a mutant and wild-type of unknown entity is maintained (see paragraph bridging pages 4-5 of the previous office action). It appears Applicant attempted to address the rejection, however, due to the lack of clarity of the language used, the amendment fails to overcome the rejection. For example, steps (e) and (g) do not recite what "the mutant" is a mutant of (i.e. a vertebrate animal). This is made further unclear by grammatical errors such as the phrase "wild type of the vertebrate animal".

New grounds of rejection under 35 U.S.C. 112, second paragraph are set forth below:

Claim 8 is unclear because the metes and bounds of the phrase "around the crosslinked site in a genome" are not clear. It is not clear how far from the crosslinked site is encompassed by the term "around". Claims 10-12 depend from claim 8.

Claims 8,13 and 18 are unclear because the metes and bounds of the term "plurality" are not clear. It is unclear if the claims encompassing a deletion of 2-3 base pairs, 100 base pairs or several kilobase pairs. Claims 10-12 depend from claim 8. Claims 15-17 depend from claim 13. Claims 20-22 depend from claim 18.

Claims 8,13 and 18 recite the limitation "the fertilized eggs" in line 8. There is insufficient antecedent basis for this limitation in the claim. Line 6 of the claim refers to fertilizing an egg, but not multiple eggs. Claims 10-12 depend from claim 8. Claims 15-17 depend from claim 13. Claims 20-22 depend from claim 18.

Claims 12,17 and 22 are indefinite because of the phrase "region containing a pyrimidine base". The metes and bounds of the phrase and its implication as a claim limitation are not clear. Ion light of the teachings of the specification, it is not clear if the limitation is limiting the mutation to alteration of a pyrimidine or that the region where a mutation is introduced must merely have a pyrimidine.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8,10-13,15-18 and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chakrabarti et al (Genetics, 1983, 103: 109-123), Grunwald et al #1 (Genet.

Res., 1991, 59: 93-101) and Grunwald et al #2 (Genet. Res., 1991, 59: 103-116) taken with Thomas et al (Mol. Cell. Biol., 1996, 16(5): 2537-2544). The rejection is maintained for reasons of record set forth on pages 5-8 of the previous office action.

Applicant has amended the claims to read that a small deletion of a plurality of bases results in the resulting animal obtained by the methods.

Thomas teaches the newly added claim limitation of a "small deletion of a plurality of base pairs" in teaching "deletions of more than one nucleotide" (see Thomas, page 2540, col. 1, last paragraph).

Applicant has argued that one skilled in the art would not have been motivated by the teachings of Thomas to select psoralen derivatives as a mutagen for vertebrate sperm in view of the variety of known mutagens available in the art.

In response, Applicant fails to substantiate this argument and it is not evident that the skilled artisan would not be motivated to use psoralen derivatives. On the contrary, as set forth in the previous office action, there is motivation to use the methods of Thomas to mutagenize vertebrate sperm (see pages 7-8 of the previous office action). Mutagens such as psoralens, particularly 4,5', 8-trimethylpsoralen, were routinely used mutagens in the art, as evidenced by Thomas. While Thomas did not use psoralens to mutagenize vertebrate sperm, the mutagenesis of vertebrate sperm was routinely performed in the art (see Chakrabarti, Grunwald #1 and Grunwald #2). The use of mutagens resulting in deletions was taught by Chakrabarti and Grunwald #1, however, these deletions resulted in large deficiencies that removed multiple genomic loci, adding a additional level of difficulty to mutant characterization. The teachings of Thomas demonstrating small deletions resulting from psoralen treatment and providing a

beneficial alternative to gamma and UV irradiation taught by Chakrabarti and Grunwald #1 that created such large genomic deficiencies. The DNA mutagenized by Thomas is of the same chemical composition as that of the instant invention and there would be no reason to believe that the teachings of Thomas could not be applied to vertebrate sperm, rendering unfounded Applicant's argument with respect to lack of motivation to apply Thomas to vertebrate sperm in light of other mutagens known in the art.

Accordingly, the previous rejection is maintained for reasons of record.

New grounds of rejection under 35 U.S.C. 103(a) are set forth below:

Claims 8,10-13,15-18 and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chakrabarti et al (Genetics, 1983, 103: 109-123), Grunwald et al #1 (Genet. Res., 1991, 59: 93-101) and Grunwald et al #2 (Genet. Res., 1991, 59: 103-116) taken with Yandell et al (PNAS, 1994, 91, pages 1381-1385; IDS).

The claims are directed to methods of mutating a gene or analyzing the function of a mutated gene of a vertebrate animal comprising treating a germ cell with a psoralen derivative, irradiating the germ cell with a high-energy beam, and subjecting the germ cell to artificial fertilization.

Chakrabarti et al teach a method of mutating genes in the zebrafish genome comprising providing sperm collected from a zebrafish, irradiating the collected sperm with γ-rays, and fertilizing isolated zebrafish oocytes with the irradiated sperm, to produce a zebrafish embryo whose genome comprises mutated genes. See page 110. In particular, Chakrabarti et al correlated the effects of mutating the gol-1 gene with a mutant phenotype; the mutant gol-1 zebrafish comprise both pigmented and unpigmented patches in the retina of the eye. See pages

114-115. Grunwald et al #1 teach similar methods to those of Chakrabarti with the main difference being use of UV light irradiation as a mutagen instead of γ-ray irradiation. See page 94. Grunwald et al #1 and Chakrabarti correlated the effects of mutating the gol-1 gene with a mutant phenotype; the mutant gol-1 zebrafish comprise both pigmented and unpigmented patches in the retina of the eye. See pages 95-96. Grunwald et al #2 teach similar methods to those of Chakrabarti and Grunwald #1 with the main difference being use of ethylnitrosourea (ENU) as a mutagen rather than UV light or γ-ray irradiation. See pages 104-105. Grunwald et al #2 as Chakrabarti and Grunwald #1 correlated the effects of mutating the gol-1 gene with a mutant phenotype; the mutant gol-1 zebrafish comprise both pigmented and unpigmented patches in the retina of the eye. See pages 110-112. The collective teachings of Chakrabarti, Grunwald #1, and Grunwald #2 set forth the use of different mutagens for inducing germline mutations in zebrafish for the purpose of analyzing gene function in zebrafish.

The collective teachings of Chakrabarti, Grunwald #1, and Grunwald #2 differ from the claimed invention, as they do not teach use of a psoralen derivative, particularly 4, 5', 8-trimethylpsoralen, as a mutagen to cause small deletions including a plurality of base pairs.

However at the time the claimed invention was made, use of psoralen derivatives as mutagens was within the purview of the ordinary artisan. In particular, Yandell et al taught the use of psoralens as mutagenic compounds to induce and analyze mutation in the animal C. elegans. Yandell et al specifically taught use of 4, 5', 8-trimethylpsoralen and UV light to induce mutations in C. elegans genomic DNA. See throughout the entire document. Yandell et al taught that mutations induced by psoralen in the experiments include small deletions. Yandell also taught that other investigators have obtained small deletions using psoralen wherein the

deletions span 1.5-1.7 kbp (see paragraph bridging col. 1-2, page 1383; page 1384, col. 1, last paragraph). The teachings of Yandell suggest psoralens, particularly 4, 5', 8-trimethylpsoralen, represent a class of mutagens capable of inducing small deletions comprising a plurality of base pairs. Yandell taught that psoralen induced mutations contrast to those induced by ENU in that ENU rarely induces a deletion. Yandell also contrasts psoralen to γ-ray and x-ray irradiation in that these other mutagens can result in larger deficiencies involving multiple loci (page 1383, col. 2). Yandell taught explicitly that psoralen mutagenesis may provide a better method than γ-ray or x-ray mutagenesis for induction of small delietions (page 1384, col. 1, last paragraph).

Thus, it would have been obvious to use the specific methods of mutagenesis taught by Yandell et al in the general methods taught by Chakrabarti, Grunwald #1, and Grunwald #2 to produce smaller alterations to the genome than are produced using γ-ray , x-ray irradiation or ENU. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as it was an art-recognized goal to mutate genes of zebrafish for analyzing gene function in zebrafish as discussed by Chakrabarti, Grunwald #1, and Grunwald #2 and to overcome the art recognized deficiencies involved with ENU, γ-ray and x-ray irradiation. A reasonable level of success would be expected in combining these references because the genome of zebrafish and other vertebrate animals comprises DNA of the same chemical makeup with similar repair mechanisms as *C. elegans* and would be expected to react similarly to psoralen mutagens.

Thus, the claimed invention, as a whole, was clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
Art Unit 1632

Joe Woitach
AU1632